L1 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1983:427998 CAPLUS
DOCUMENT NUMBER: 99:27998
TITLE: Storage-stable, crosslinked hemoglobin preparation with high oxygen transport capacity
INVENTOR(S): Bonhard, Klaus; Kothe, Norbert
PATENT ASSIGNEE(S): Biotest-Serum-Institut G.m.b.H., Fed. Rep. Ger.
SOURCE: Ger. Offen., 25 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 3144705	A1	19830519	DE 1981-3144705	19811111
DE 3144705	C2	19831208		
EP 78961	A2	19830518	EP 1982-109808	19821023 <--
EP 78961	A3	19830727		
EP 78961	B1	19861015		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
AT 22803	E	19861115	AT 1982-109808	19821023
JP 58135818	A2	19830812	JP 1982-193572	19821105
JP 03065326	B4	19911011		
US 4777244	A	19881011	US 1987-47819	19870508

PRIORITY APPLN. INFO.:
DE 1981-3144705 19811111
EP 1982-109808 19821023
US 1982-439473 19821105

AB A blood substitute is prepd. by treating a stroma-free Hb soln. with an O-consuming reducing agent (neutralized ascorbic acid) to reduce the pO2 to 0 mbar, mixing with a biol. effector (pyridoxal phosphte or inositol hexaphosphate), and crosslinking with a C3-8 dialdehyde at pH 6-8. The product was reduced with a carbonyl-specific reagent (NaBH4), dild. with H2O, treated with activated C, and ultrafiltered. The product can be stabilized with a reducing agent. Thus, an ultrafiltered Hb soln. contg. 19.6% Hb was added to a 4-fold molar excess of neutralized ascorbic acid, sterilized by filtration, and allowed to stand 24 h. The soln., 842 mL, was cooled, mixed with NaH2PO4-Na2HPO4 and 2.2 g pyridoxal phosphate for 1 h, and then 13.9 mL 10% glutaraldehyde was stirred in for 1 h, followed by 1.34 g NaBH4. The foaming soln. was dild. with 6 L H2O after 30 min, treated with 10 g activated C/L for 1 h, and filtered. The soln. was concd. by ultrafiltration to 10-11%, and mixed with 115 mL 20 human albumin to adjust osmotic pressure, and then with NaCl 3.32, glucose 14.5, NaHCO3 1.66, KCl 0.26, MgSO4 0.16, and neutralized ascorbic acid 0.61 g before sterilization by filtration. The product was 660 mL of a soln. contg. 8.5% Hb and 5.1% relative met-Hb.

IT Blood substitutes and Plasma expanders
(Hb reaction products with inositol hexaphosphate or pyridoxal phosphate prepn. and formulation for)

IT Hemoglobins
RL: PREP (Preparation)
(reaction products with inositol hexaphosphate or pyridoxal phosphate, crosslinked reduced, prepn. and formulation of, for blood substitutes)

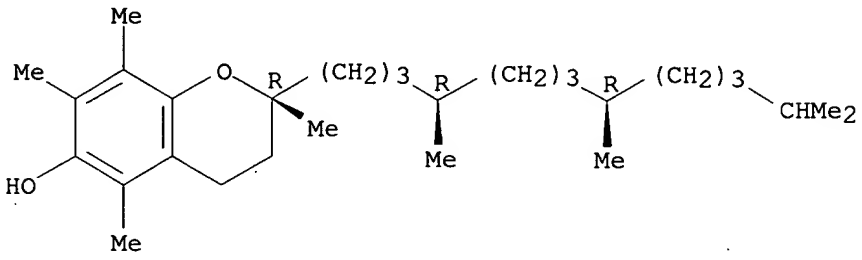
IT 54-47-7DP, reaction products with Hb 83-86-3DP, reaction products with Hb
RL: PREP (Preparation)
(crosslinked, prepn. and formulation of, for blood substitutes)

=>

L4 ANSWER 113 OF 113 REGISTRY COPYRIGHT 2003 ACS
RN 58-95-7 REGISTRY
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, acetate, (2R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **.alpha.-Tocopherol acetate (6CI)**
CN 2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-, acetate, [2R-[2R*(4R*,8R*)]]-
CN 6-Chromanol, 2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-, acetate, (+)- (8CI)
CN Vitamin E acetate (7CI)
OTHER NAMES:
CN **(+)-.alpha.-Tocopherol acetate**
CN (+)-.alpha.-Tocopheryl acetate
CN **(2R,4'R,8'R)-.alpha.-Tocopherol acetate**
CN (2R,4'R,8'R)-.alpha.-Tocopheryl acetate
CN (R,R,R)-.alpha.-Tocopheryl acetate
CN .alpha.-Tocopheryl acetate
CN 2,5,7,8-Tetramethyl-2-(4,8,12-trimethyltridecyl)-6-chromanol acetate
CN Alfacol
CN Combinal E
CN Contopheron
CN Copherol 12250
CN Copherol 1250
CN Covitol 1100
CN Covitol 1360
CN **D-.alpha.-Tocopherol acetate**
CN **d-.alpha.-Tocopherol acetate**
CN D-.alpha.-Tocopheryl acetate
CN d-.alpha.-Tocopheryl acetate
CN d-Vitamin E acetate
CN E-Ferol
CN E-Toplex
CN E-Vicotrat
CN Ecofrol
CN Econ
CN Endo E Dompe
CN Ephynal acetate
CN Epsilan-M
CN Erevit
CN Evipherol
CN Fertilvit
CN Gevex
CN Spondyvit
CN Tinoderm E
CN Tocopherex
CN Tocopherol acetate
CN Tocopheryl acetate
CN Tocophrin
CN Tofaxin
CN Tokoferol acetate
CN Vitamin E.alpha. acetate
FS STEREOSEARCH
DR 12741-00-3, 1406-70-8, 26243-95-8
MF C31 H52 O3
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DETHERM*, DIOGENES, EMBASE, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PIRA, PROMT, RTECS*, SPECINFO, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)

(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

11570 REFERENCES IN FILE CA (1962 TO DATE)
170 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
11596 REFERENCES IN FILE CAPLUS (1962 TO DATE)
17 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

hemocyanin

L4 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1992:566037 CAPLUS
DOCUMENT NUMBER: 117:166037
TITLE: Inhibition of lipid peroxidation promoted by iron(III) and ascorbate
AUTHOR(S): Beach, Dorothy C.; Giroux, Eugene
CORPORATE SOURCE: Marion Merrell Dow Res. Inst., Cincinnati, OH, 45215, USA
SOURCE: Archives of Biochemistry and Biophysics (1992), 297(2), 258-64
CODEN: ABBIA4; ISSN: 0003-9861
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Peroxidn. of rat liver microsomes and of phospholipid isolated from them was studied using iron(III) and ascorbate initiation. One-half equiv. of citrate per iron equiv. maintained soly. of the metal ion at neutral pH. Several metal chelators, including addnl. citrate, blocked preoxidn., but catalase did not. These characteristics are consistent with those reported by others (D. M. Miller and S. D. Aust, 1989). Several **antioxidants**, principally tocopherol analogs and **nitroxides**, and, as well, a nonenzymic component of thymol-free catalase, potently blocked lipid peroxidn., or, equivalently, dioxygen depletion from suspensions of peroxidizing microsomes. Chromanols were the most active **antioxidants**. No thiol studied had significant **antioxidant** activity in the test system.

L4 ANSWER 3 OF 8 MEDLINE
ACCESSION NUMBER: 97117066 MEDLINE
DOCUMENT NUMBER: 97117066 PubMed ID: 8958151
TITLE: Influence of structure on the **antioxidant** activity of indolinic **nitroxide** radicals.
AUTHOR: Antosiewicz J; Damiani E; Jassem W; Wozniak M; Orena M; Greci L
CORPORATE SOURCE: Department of Bioenergetics, Academy of Physical Education, Gdansk, Poland.
SOURCE: FREE RADICAL BIOLOGY AND MEDICINE, (1997) 22 (1-2) 249-55. Journal code: 8709159. ISSN: 0891-5849.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970422
Last Updated on STN: 19970422
Entered Medline: 19970410

AB An in vitro study was carried out to verify whether the chain length of a substituent on an indolinic **nitroxide** could influence its **antioxidant** activity in different biological environments subjected to oxidative stress. Three distinct indolinic **nitroxides** were synthesized and compared with vitamin E and **Trolox** (a hydrophilic analogue of vitamin E), where the only difference between the **nitroxides** was the length of the hydrocarbon chain in the 2-position of indole, namely 2 (C2), 10 (C10), and 18 (C18) carbons. All the **nitroxides** were effective in preventing oxidation of bovine serum albumin, but to different extents, with the longer chain derivatives being more efficient. However, the C2 compound was the most efficient in preventing lipid peroxidation in microsomal membranes. The C2 and C18 compounds, **Trolox**, and vitamin E protected microsomal protein oxidation to the same extent at the highest concentration used (13 microM). The **nitroxide** with a C10 chain was less effective in this system. The influence of these compounds on the enzymatic activity of two mitochondrial proteins subjected to oxidative stress was also studied by means of oxygraph measurements. Mitochondrial rotenone-sensitive NADH oxidase and succinate oxidase responded differently to BuOOH-induced radical chemistry, and the compounds under study also protected the activity of the two enzymes but to different extents. The results clearly demonstrate that indolinic **nitroxides** are very efficient **antioxidants**, protecting both lipids and proteins from peroxidation. The indole structure influences the **antioxidant** efficacy in biologi

7 ANSWER 4 OF 18 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1999345778 MEDLINE
DOCUMENT NUMBER: 99345778 PubMed ID: 10409186
TITLE: Detection of a ferrylhemoglobin intermediate in an endothelial cell model after hypoxia-reoxygenation.
AUTHOR: McLeod L L; Alayash A I
CORPORATE SOURCE: Division of Hematology, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, Maryland 20892, USA.
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1999 Jul) 277 (1 Pt 2) H92-9.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990913
Last Updated on STN: 19990913
Entered Medline: 19990830

AB A cell culture model of bovine aortic endothelial cells attached to microcarrier beads was used to study the interaction of diaspirin **cross-linked hemoglobin** (an oxygen-carrying blood substitute) with hypoxia-reoxygenation. **Hemoglobin** (200 microM) and hypoxia-volume restriction (3-5 h), together and separately, caused toxicity in this model, as measured by decreased cellular replating efficiency. **Hemoglobin** (60 microM) caused a reduction in hydrogen peroxide concentration and an increase in lipid peroxidation above that induced by hypoxia alone. Incubation of **hemoglobin** with endothelial cells caused transient oxidation of **hemoglobin** to its highly reactive and toxic ferryl species after >/=3 h of hypoxia, followed by 1 h of reoxygenation. Lipid peroxidation, which may occur in the presence of ferrylhemoglobin, also occurred after 1 h of reoxygenation. **Hemoglobin** caused a dose-dependent decrease in intracellular glutathione concentration, suggesting that it caused an oxidative stress to the cells. However, addition of ascorbate, alpha-tocopherol, or **trolox** did not decrease **hemoglobin** oxidation in the presence of normal or hypoxic cells. It is concluded that diaspirin **cross-linked hemoglobin** forms a ferryl intermediate in the absence of any exogenously added oxidant and contributes to the oxidative burden experienced by endothelial cells after hypoxia-reoxygenation, a condition that is likely to be encountered during trauma and surgery when **hemoglobin** solutions are used as perfusion agents.

ACCESSION NUMBER: 2001:490417 CAPLUS
DOCUMENT NUMBER: 135:269564
TITLE: Initiation and inhibition of free radical processes in H2O2-metmyoglobin (methemoglobin)-2,2'-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) systems
AUTHOR(S): Metelitza, D. I.; Eryomin, A. N.; Sviridov, D. O.; Kamyshnikov, V. S.
CORPORATE SOURCE: Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Minsk, 220141, Belarus
SOURCE: Biochemistry (Moscow, Russian Federation)(Translation of Biokhimiya (Moscow, Russian Federation)) (2001), 66(5), 505-514
CODEN: BIORAK; ISSN: 0006-2979
PUBLISHER: MAIK Nauka/Interperiodica Publishing
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Rates of free radical initiation were detd. at 20.degree. in 10 mM phosphate buffer (pH 7.4) in the systems metmyoglobin (metHb)-H2O2 using 2,2'-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) as the diammonium salt (ABTS). The catalytic activity of MetMb was 2-3-fold higher than that of MetHb. The process can be described by the Michaelis-Menten equation, from which effective values of Km and Vmax were calcd. Comparative kinetic studies on the inhibition of ABTS oxidn. were carried out using **Trolox**, propylgallate (PG), polydisulfide of gallic acid (poly(DSG)), polydisulfide of (2-amino-4-nitrophenol) (poly(ADSNP)), and its **conjugate** with human serum albumin (HSA-poly(ADSNP)). The inhibitors were characterized by inhibition consts. Ki and stoichiometric inhibition coeffs. f (the no. of radicals terminated by a single mol. of inhibitor). The min. Ki and the max. f values were obtained for poly(DSG), and in the system of MetHb-H2O2-ABTS they were 0.08 .mu.M and 27.5, resp. According to their antiradical activities, the inhibitors can be arranged as follows: poly(DSG) > poly(ADSNP) > PG > **Trolox**, PG, poly(DSG), poly(ADSNP), and its **conjugate** with HSA are suggested as "calibrators", i.e., inhibition stds. for evaluation of antioxidant status of biol. fluids in possible test systems based on the free radical-generating pair MetMb-H2O2 with ABTS as the acceptor of the active radicals.

IT Antioxidants
Radical scavengers
Reaction kinetics
(initiation and inhibition of free radical processes in H2O2-metmyoglobin (metHb)-2,2'-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) systems)

IT **Hemoglobins**, methemoglobins
Myoglobins, metmyoglobins
RL: BPR (Biological process); BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); PROC (Process); RACT (Reactant or reagent)
(initiation and inhibition of free radical processes in H2O2-metmyoglobin (metHb)-2,2'-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) systems)

IT Radicals, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent)
(initiation and inhibition of free radical processes in H2O2-metmyoglobin (metHb)-2,2'-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) systems)

IT 7722-84-1, Hydrogen peroxide, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); PROC (Process); RACT (Reactant or

reagent)
(initiation and inhibition of free radical processes in H2O2-metmyoglobin (metHb)-2,2'-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) systems)

IT 121-79-9, Propylgallate **53188-07-1, Trolox** 204994-78-5 255059-06-4
RL: BUU (Biological use, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(initiation and inhibition of free radical processes in H2O2-metmyoglobin (metHb)-2,2'-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) systems)

IT 255059-06-4DP, human serum albumin **conjugate** derivs.
RL: BUU (Biological use, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(initiation and inhibition of free radical processes in H2O2-metmyoglobin (metHb)-2,2'-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) systems)

IT 28752-68-3, ABTS
RL: RCT (Reactant); RACT (Reactant or reagent)
(initiation and inhibition of free radical processes in H2O2-metmyoglobin (metHb)-2,2'-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) systems)

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 18 CAPLUS

L11 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:124515 CAPLUS
DOCUMENT NUMBER: 120:124515
TITLE: Chemical syntheses of Trolox conjugates which protect human ventricular myocytes against in situ-generated oxyradicals
AUTHOR(S): Zielenski, Julian; Wu, Tai Wing; Fung, Kwok Pui; Zeng, Ling Hua; Li, Ren Ki; Mickle, Donald A. G.; Wu, Jun
CORPORATE SOURCE: Dep. Clin. Biochem., Univ. Toronto, Toronto, ON, M5G 2C4, Can.
SOURCE: European Journal of Pharmacology, Environmental Toxicology and Pharmacology Section (1993), 248(4), 313-18
CODEN: EPEPEG; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Synthetic conjugates of the antioxidant Trolox (6-hydroxy-2,5,7,8-tetramethyl chroman-2-carboxylic acid) have been prepd. by coupling it with 1-ethyl-3-(3-dimethyl-amino-propyl) carbodiimide hydrochloride either to p-aminophenyl-.beta.-D-lactopyranoside, or to higher mol. wt. ligands such as **dextran** and polylysine. Compared to Trolox and on a mole to mole basis, **dextran**-Trolox is almost equally active, while lactosylphenyl- and polylysine-Trolox conjugates are distinctly more active in preventing the damage on human ventricular myocytes by oxyradicals generated from xanthine oxidase-hypoxanthine. Listed in order of decreasing cytoprotective activity, they are: lactosylphenyl-Trolox .mchgt. polylysine-Trolox > Trolox > **dextran**-Trolox. Thus, Trolox can be chem. modified by coupling it to one of a no. of ligands and, in some cases, with resultant increases in its ability to protect human ventricular myocytes from oxyradical damage.

L13 ANSWER 11 OF 13 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 96429662 MEDLINE
DOCUMENT NUMBER: 96429662 PubMed ID: 8832763
TITLE: Effect of **Trolox** C on the oxygenation reaction of prostaglandin endoperoxide synthase with cis,cis-eicosa-11, 14-dienoic acid.
AUTHOR: Bakovic M; Dunford H B
CORPORATE SOURCE: Department of Chemistry, University of Alberta, Edmonton, Canada.
SOURCE: PROSTAGLANDINS LEUKOTRIENES AND ESSENTIAL FATTY ACIDS, (1996 May) 54 (5) 341-9.
Journal code: 8802730. ISSN: 0952-3278.
PUB. COUNTRY: SCOTLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961218

AB **Trolox** C, a water-soluble derivative of alpha-**tocopherol**, stimulates the oxygenation of cis,cis-eicosa-11, 14-dienoic acid (AH) by prostaglandin endoperoxide synthase at lower concentrations and suppresses the stimulated reaction at higher concentrations. Surprisingly, **Trolox** C does not affect the stoichiometric ratio between the rate of formation of the oxygenation product 11-hydroxy-12-trans, 14-cis-eicosadienoic acid (AOH) and the rate of disappearance of molecular oxygen. The ratio of the two rates, d[AOH]/-d[O2], remains constant at 2/1 for a series of **Trolox** C concentrations and in the absence of **Trolox** C. Results indicate that AH reacts preferentially with Compound I of the enzyme and that **Trolox** C does not compete for Compound I. Enzyme inactivation begins with formation of an unproductive Compound I-tyrosyl radical (Compound I-X.) which has the same number of oxidizing equivalents as the conventional peroxidase Compound I. The stimulating effect of low concentrations of **Trolox** C can be explained by reduction of the oxyferryl **heme** so that Compound I-X. is reduced to a Compound II-X.species, the Compound II analog of Compound I-X.. Thus **heme** bleaching is prevented. A further one-electron reduction by **Trolox** C of Compound II-X. reforms the native enzyme, which permits enzyme recycling. Large concentrations of **Trolox** C inhibit reformation of native enzyme, reducing the extent of stimulation.

CCESSION NUMBER: 2001236216 MEDLINE
DOCUMENT NUMBER: 21231834 PubMed ID: 11334023
TITLE: Antioxidant status and oxidative stress in elite alpine ski racers.
AUTHOR: Subudhi A W; Davis S L; Kipp R W; Askew E W
CORPORATE SOURCE: Orthopedic Specialty Hospital, Salt Lake City, UT 84107, USA.
SOURCE: INTERNATIONAL JOURNAL OF SPORT NUTRITION AND EXERCISE METABOLISM, (2001 Mar) 11 (1) 32-41.
Journal code: 100939812. ISSN: 1526-484X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010604
Last Updated on STN: 20010604
Entered Medline: 20010531
AB The goal of this study was to access antioxidant status and markers of oxidative damage in elite alpine ski racers during routine training. Subjects included 12 members of the U.S. Men's Alpine Ski Team attending a 10-day summer training camp. Blood draws were collected at rest and after exercise: (a) prior to training, (b) following 2 days of dry land training, and (c) after 4 days of on-snow skiing. Seven measures of antioxidant status were determined using colorimetric and HPLC methods (**Trolox** equivalent antioxidant capacity, uric oxidase, alpha-**tocopherol**, total glutathione, cytosolic glutathione peroxidase, and superoxide dismutase). Oxidative stress was assessed using 2 markers of lipid oxidation (malondialdehyde and lipid hydroperoxides) and 2 markers of protein oxidation (carbonylated total proteins and carbonylated **hemoglobin**). The results of this study suggest that antioxidant status of elite alpine skiers may decline over a period of intense training. However, elevations in markers of oxidative stress were not evident.

ACCESSION NUMBER: 1998325679 MEDLINE
DOCUMENT NUMBER: 98325679 PubMed ID: 9661202
TITLE: Polyhemoglobin-superoxide dismutase-catalase as a blood substitute with **antioxidant** properties.
COMMENT: Comment in: Nat Biotechnol. 1998 Jul;16(7):621-2
AUTHOR: D'Agnillo F; Chang T M
CORPORATE SOURCE: Artificial Cells and Organs Research Centre, Faculty of Medicine, McGill University, Montreal, Canada.
SOURCE: NATURE BIOTECHNOLOGY, (1998 Jul) 16 (7) 667-71. Journal code: 9604648. ISSN: 1087-0156.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981021
Last Updated on STN: 19981021
Entered Medline: 19981015

AB Polyhemoglobin-superoxide dismutase-catalase is designed to function as an oxygen carrier with **antioxidant** properties. This is based on cross-linking **hemoglobin** with superoxide dismutase and catalase (PolyHb-SOD-CAT). This study describes the structural and **antioxidant** properties of this solution. Our studies show that superoxide dismutase and catalase retain their enzymatic activity following glutaraldehyde polymerization with 8:1 and 16:1 glutaraldehyde: **hemoglobin** ratio. We have analyzed the optimal SOD/CAT ratios to prevent oxidation of **hemoglobin** in the presence of oxygen free radicals. The circulation half-life of **crosslinked hemoglobin**, SOD, and catalase in Sprague-Dawley rats correlates with the degree of polymerization as determined by high-performance molecular weight gel filtration. PolyHb-SOD-CAT decreases the formation of oxygen radicals compared with PolyHb in a rat intestinal ischemia-reperfusion model.

L18 ANSWER 88 OF 187 MEDLINE

ACCESSION NUMBER: 2000094382 MEDLINE
DOCUMENT NUMBER: 20094382 PubMed ID: 10630686
TITLE: **Hemoglobin** and iron-evoked oxidative stress in the brain: protection by bile pigments, manganese and S-nitrosoglutathione.
AUTHOR: Van Bergen P; Rauhala P; Spooner C M; Chiueh C C
CORPORATE SOURCE: Unit on Neurodegeneration and Neuroprotection, Laboratory of Clinical Science, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892-1264, USA.
SOURCE: FREE RADICAL RESEARCH, (1999 Dec) 31 (6) 631-40. Journal code: 9423872. ISSN: 1071-5762.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000320
Last Updated on STN: 20000320
Entered Medline: 20000303

AB In the present in vitro and in vivo study we investigated the pro-oxidant effects of **hemoglobin**, as well as the **antioxidant** effects of its metabolites, in the brain. Incubation of rat brain homogenates with **hemoglobin** (0-10 microM) but not hemin induced lipid peroxidation up to 24 h (EC50 = 1.2 microM). **Hemoglobin**'s effects were similar to ferrous ion (EC50 = 1.7 microM) and were blocked by the chelating agent deferoxamine (IC50 0.5 microM) and a nitric oxide-releasing compound S-nitrosoglutathione (IC50 = 40 microM). However, metabolites of **hemoglobin** - biliverdin and bilirubin - inhibited brain lipid peroxidation induced by cell disruption and **hemoglobin** (biliverdin IC50 = 12-30 and bilirubin IC50 = 75-170 microM). Biliverdin's antioxidative effects in spontaneous and iron-evoked lipid peroxidation were further augmented by manganese (2 microM) since manganese is an antioxidative transition metal and **conjugates** with bile pigments. Intrastriatal infusion of **hemoglobin** (0-24 nmol) produced slight, but significant 20-22% decreases in striatal dopamine levels. Whereas, intrastriatal infusion of ferrous citrate (0-24 nmol) dose-dependently induced a greater 66% deplètion of striatal dopamine which was preceded by an acute increase of lipid peroxidation. In conclusion, contrary to the in vitro results **hemoglobin** is far less neurotoxic than ferrous ions in the brain. It is speculated that **hemoglobin** may be partially detoxified by heme oxygenase and biliverdin reductase to its antioxidative metabolites in the brain. However, in head trauma and stroke, massive bleeding could significantly produce iron-mediated oxidative stress and neurodegeneration which could be minimized by endogenous **antioxidants** such as biliverdin, bilirubin, manganese and S-nitrosoglutathione.

L18 ANSWER 31 OF 187 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:407793 CAPLUS
DOCUMENT NUMBER: 136:161291
TITLE: Quercetin diminishes the binding of **hemoglobin** to the red blood cell membrane
AUTHOR(S): Cesquini, M.; Tenor, A. C.; Torsoni, M. A.; Stoppa, G. R.; Pereira, A. L.; Ogo, S. H.
CORPORATE SOURCE: Departamento de Bioquimica, Instituto de Biologia, Universidade Estadual de Campinas, Campinas, Brazil
SOURCE: Journal of Anti-Aging Medicine (2001), 4(1), 55-63
CODEN: JAMEF8; ISSN: 1094-5458
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Hb** oxidn. leads to the formation of hemichrome, which binds to the membrane and causes red blood cell removal by the reticuloendothelial system. In the present investigation, the effect of flavonoids on **Hb** oxidn. and their binding to red blood cell (RBC) membranes were studied using tert-Bu hydroperoxide (tert-BOOH) to promote oxidative stress. The intrinsic **antioxidant** activity of RBC was able to prevent the binding of **Hb** to the membrane at tert-BOOH concns. .ltoreq.0.4 mM. At higher concns., a brown pellet was obsd. and represented the appearance of membrane-**bound** oxidized **Hb** . Oxidns. performed in membrane-free **Hb** solns. with an identical oxidative system showed less **Hb** oxidn. These observations suggest that erythrocyte membrane lipid peroxidn. enhances the oxidative damage of **Hb**, increasing its binding to membranes. Quercetin partially protected **Hb** against oxidn. by tert-BOOH and reduced the levels of the membrane **bound** hemichrome. Lipid peroxidn. was also significantly suppressed by quercetin. Rutin and morin had little effect in preventing **Hb** binding to RBC membranes, indicating the importance of structure in the **antioxidant** properties of flavonoids. In the absence of oxidant, the peroxidn. of erythrocyte membrane and isotonic hemolysis were protected by quercetin. These results suggest that quercetin displays a beneficial role on aging of RBC.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 25 OF 187 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:879831 CAPLUS
DOCUMENT NUMBER: 135:142034
TITLE: A novel **hemoglobin**-adenosine-glutathione based blood substitute: Evaluation of its effects on human blood ex vivo
AUTHOR(S): Simoni, Jan; Simoni, Grace; Wesson, Donald E.; Griswold, John A.; Feola, Mario
CORPORATE SOURCE: Department of Surgery, Texas Tech University Health Sciences Center, Lubbock, TX, 79430, USA
SOURCE: ASAIO Journal (2000), 46(6), 679-692
CODEN: AJOUET; ISSN: 1058-2916
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Chem. modified **Hb** solns. are under current investigation as potential red cell substitutes. Researchers at Texas Tech University have developed a novel free **Hb** based blood substitute product. This blood substitute is composed of purified bovine **Hb** **cross-linked** intramolecularly with o-adenosine-5'-triphosphate and intermolecularly with o-adenosine, and **conjugated** with reduced glutathione (GSH). In this study, we compared the effects of our novel blood substitute and unmodified (U) **Hb**, by using allogenic plasma as the control, on human blood components: red blood cells (RBCs), platelets, monocytes (Mo), and low-d. lipoproteins (LDLs). The pro-oxidant potential of both **Hb** solns. on RBCs was examd. by the measurement of osmotic and mech. fragility, **conjugated** dienes (CD), lipid hydroperoxides (LOOH), thiobarbituric acid reactants (TBAR-S), isoprostanes (8-iso PGF2.alpha.) and intracellular GSH. The oxidative modification of LDLs was assessed by CD, LOOH, and TBAR-S, and the degree of apolipoprotein (apo) B crosslinking. The effects of **Hb** on platelets have been studied by monitoring their responses to the aggregation agonists: collagen, ADP, epinephrine, and arachidonic acid. Monocytes were cultured with **Hb** solns. or plasma and tested for TNF-.alpha. and IL-1.beta. release, then examd. by electron microscopy. Results indicate that native UHb initiates oxidative stress of many blood components and aggravates inflammatory responses of Mo. It also caused an increase in RBC osmotic and mech. fragility ($p < 0.001$). While the level of GSH was slightly changed, the lipid peroxidn. of RBC increased ($p < 0.001$). UHb was found to be a stimulator of 8-iso PGF2.alpha. synthesis, a potent modulator of LDLs, and an effective potentiator of agonist induced platelet aggregation. Contrarily, our novel blood substitute did not seem to induce oxidative stress nor to increase Mo inflammatory reactions. The osmotic and mech. fragility of RBCs was similar to that of the control. Such modified **Hb** failed to alter LDLs, increase the prodn. of 8-iso PGF2.alpha., but markedly inhibited platelet aggregation. The effect of this novel blood substitute can be **linked** with the cytoprotective and anti-inflammatory properties of adenosine, which is used as a crosslinker and surface modifier, and a modification procedure that lowers the **Hb** pro-oxidant potential.

REFERENCE COUNT: 100 THERE ARE 100 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

CCESSION NUMBER: 1994:260894 CAPLUS
DOCUMENT NUMBER: 120:260894
TITLE: **Cross-linked hemoglobin** -superoxide dismutase-catalase scavenges oxygen-derived free radicals and prevents methemoglobin formation and iron release
AUTHOR(S): D'Agnillo, F.; Chang, Thomas M.S.
CORPORATE SOURCE: Fac. Med., McGill Univ., Montreal, QC, H3G 1Y6, Can.
SOURCE: Biomaterials, Artificial Cells, and Immobilization Biotechnology (1993), 21(5), 609-21
CODEN: BACBEU; ISSN: 1055-7172
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In this study, the authors prepd. PolyHb-SOD-catalase (intermolecularly **cross-linked Hb**, superoxide dismutase (SOD), and catalase). The authors found that PolyHb-SOD-catalase is effective in scavenging oxygen-derived free radicals. In the xanthine/xanthine oxidase system, the initial rate of cytochrome c redn. was 2.13 .+-. 0.26 nmoles/min for PolyHb alone. PolyHb-SOD-catalase reduced this to 0.56 .+-. 0.08 nmoles/min because of its ability to eliminate superoxide (O2-). Addn. of PolyHb to 200 .mu.M of hydrogen peroxide (H2O2), changed the H2O2 level slightly to 192 .+-. 0.4 .mu.M. Addn. of PolyHb-SOD-catalase, on the other hand, lower the level to 41 .+-. 0.3 .mu.M. Results also show that both effects were dependent on the concn. of SOD-catalase **cross-linked** with **Hb**. Oxidative challenge with H2O2 resulted in minimal changes in the absorbance spectra of PolyHb-SOD-catalase. With PolyHb, there were spectral changes reflecting the formation of metHb and heme degrdn. Furthermore, the amt. of iron released, after incubation with 250 .mu.M H2O2, was 6.8 .+-. 1.8 .mu.g/dL for PolyHb-SOD-catalase and 76.6 .+-. 1.0 .mu.g/dL for PolyHb. These results show that **cross-linked** SOD-catalase prevents oxidative reactions involving the **Hb** component of PolyHb-SOD-catalase.

ANSWER 8 OF 8 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1992:566037 CAPLUS
DOCUMENT NUMBER: 117:166037
TITLE: Inhibition of lipid peroxidation promoted by iron(III) and ascorbate
AUTHOR(S): Beach, Dorothy C.; Giroux, Eugene
CORPORATE SOURCE: Marion Merrell Dow Res. Inst., Cincinnati, OH, 45215, USA
SOURCE: Archives of Biochemistry and Biophysics (1992), 297(2), 258-64
CODEN: ABBIA4; ISSN: 0003-9861
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Peroxidn. of rat liver microsomes and of phospholipid isolated from them was studied using iron(III) and ascorbate initiation. One-half equiv. of citrate per iron equiv. maintained soly. of the metal ion at neutral pH. Several metal chelators, including addnl. citrate, blocked preoxidn., but catalase did not. These characteristics are consistent with those reported by others (D. M. Miller and S. D. Aust, 1989). Several **antioxidants**, principally tocopherol analogs and **nitroxides**, and, as well, a nonenzymic component of thymol-free catalase, potently blocked lipid peroxidn., or, equivalently, dioxygen depletion from suspensions of peroxidizing microsomes. Chromanols were the most active **antioxidants**. No thiol studied had significant **antioxidant** activity in the test system.

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L4 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2003 ACS
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ACCESSION NUMBER: 1992:566037 CAPLUS
DOCUMENT NUMBER: 117:166037
TITLE: Inhibition of lipid peroxidation promoted by iron(III) and ascorbate
AUTHOR(S): Beach, Dorothy C.; Giroux, Eugene
CORPORATE SOURCE: Marion Merrell Dow Res. Inst., Cincinnati, OH, 45215, USA
SOURCE: Archives of Biochemistry and Biophysics (1992), 297(2), 258-64
CODEN: ABBIA4; ISSN: 0003-9861
DOCUMENT TYPE: Journal
LANGUAGE: English
IT Thiols, biological studies
RL: BIOL (Biological study)
(lipid peroxidn. in microsomes response to, model system of)
IT Microsome
(lipid peroxidn. in, model system for, **antioxidants** inhibition of)
IT **Nitroxides**
Phenols, biological studies

RL: BIOL (Biological study)
(lipid peroxidn. of microsomes inhibition by, model system of)

IT Peroxidation
(of lipids, iron and ascorbate promotion of, **antioxidants** inhibition of)

IT Lipids, biological studies
Phospholipids, biological studies
RL: BIOL (Biological study)
(peroxidn. of, in liver microsomes, **antioxidants** inhibition of, model system for)

IT Tocopherols
RL: BIOL (Biological study)
(analogs, lipid peroxidn. of microsomes inhibition by, model system of)

IT 7782-44-7, Dioxygen, biological studies
RL: BIOL (Biological study)
(depletion of, in lipid peroxidn. model system, **antioxidants** effect on)

IT 504-17-6DP, reactive substances
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation)
(formation of, in lipid peroxidn. system of microsomes, **antioxidants** effect on)

IT 1953-02-2, N-(2-Mercaptopropionyl)glycine 23288-49-5, Probucol
62571-86-2, Captopril 87214-65-1, MDL 19327 119193-61-2, MDL 27955
119193-62-3, MDL 28365 129895-82-5, MDL 29311 143716-39-6, MDL 28963
143716-40-9, MDL 29591 143716-41-0, MDL 29752 143737-36-4, MDL 29724
RL: BIOL (Biological study)
(lipid peroxidn. in microsomes response to, model system of)

IT 89-83-8, Thymol 56305-04-5, **Trolox** 130573-32-9, MDL 73404
130573-34-1, MDL 73335 143716-38-5, MDL 73362
RL: BIOL (Biological study)
(lipid peroxidn. of microsomes inhibition by, model system of)

IT 77-92-9, Citric acid, biological studies
RL: BIOL (Biological study)
(lipid peroxidn. promotion by iron and ascorbate inhibition by, model system of)

IT 50-81-7, Ascorbic acid, biological studies
RL: BIOL (Biological study)
(lipid peroxidn. promotion by iron and, **antioxidants** inhibition of, model system for)

IT 7439-89-6, Iron, biological studies
RL: BIOL (Biological study)
(lipid peroxidn. promotion by, **antioxidants** inhibition of, model system of)

IT 9000-83-3, ATPase
RL: BIOL (Biological study)
(potassium-sodium-activating, lipid peroxidn. model system response to)

IT 9001-05-2, Catalase
RL: BIOL (Biological study)
(thymol free com., lipid peroxidn. inhibition by nonenzymic component of)

=>

ACCESSION NUMBER: 2001526614 MEDLINE
DOCUMENT NUMBER: 21228276 PubMed ID: 11330842
TITLE: Melatonin prevents delta-aminolevulinic acid-induced oxidative DNA damage in the presence of Fe2+.
AUTHOR: Qi W; Reiter R J; Tan D X; Manchester L C; Calvo J R
CORPORATE SOURCE: Department of Cellular and Structural Biology, The University of Texas Health Science Center San Antonio, 78229-3900, USA.
SOURCE: MOLECULAR AND CELLULAR BIOCHEMISTRY, (2001 Feb) 218 (1-2) 87-92.
Journal code: 0364456. ISSN: 0300-8177.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20011001
Last Updated on STN: 20011001
Entered Medline: 20010927
AB Delta-aminolevulinic acid (ALA), a **heme** precursor which accumulates during lead poisoning and acute intermittent porphyria, is reported to cause liver cancer. The carcinogenic mechanisms of ALA may relate to its ability to generate free radicals through metal-catalyzed oxidation which cause oxidative DNA damage. The aim of this study was to compare the efficacy of melatonin, **trolox** (vitamin E) and mannitol in altering DNA damage induced by ALA. Herein, we found, in the presence of Fe2+, that ALA-induced formation of 8-hydroxydeoxyguanosine in calf thymus DNA was dose and time-dependent. Melatonin, mannitol and **trolox**, all of which are free radical scavengers, inhibited the formation of 8-hydroxydeoxyguanosine in a concentration-dependent manner. The concentration of each (melatonin, mannitol and **trolox**) required to reduce DNA damage by 50%, i.e., the IC50, was 0.52, 0.84 and 0.90 mM, respectively.

L5 ANSWER 46 OF 86 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:490417 CAPLUS
DOCUMENT NUMBER: 135:269564
TITLE: Initiation and inhibition of free radical processes in H2O2-metmyoglobin (methemoglobin)-2,2'-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) systems
AUTHOR(S): Metelitza, D. I.; Eryomin, A. N.; Sviridov, D. O.; Kamyshnikov, V. S.
CORPORATE SOURCE: Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Minsk, 220141, Belarus
SOURCE: Biochemistry (Moscow, Russian Federation)(Translation of Biokhimiya (Moscow, Russian Federation)) (2001), 66(5), 505-514
CODEN: BIORAK; ISSN: 0006-2979
PUBLISHER: MAIK Nauka/Interperiodica Publishing
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Rates of free radical initiation were detd. at 20.degree. in 10 mM phosphate buffer (pH 7.4) in the systems metmyoglobin (metHb)-H2O2 using 2,2'-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) as the diammonium salt (ABTS). The catalytic activity of MetMb was 2-3-fold higher than that of MetHb. The process can be described by the Michaelis-Menten equation, from which effective values of Km and Vmax were calcd. Comparative kinetic studies on the inhibition of ABTS oxidn. were carried out using **Trolox**, propylgallate (PG), polydisulfide of gallic acid (poly(DSG)), polydisulfide of (2-amino-4-nitrophenol) (poly(ADSNP)), and its conjugate with human serum albumin (HSA-poly(ADSNP)). The inhibitors were characterized by inhibition consts. Ki and stoichiometric inhibition coeffs. f (the no. of radicals terminated by a single mol. of inhibitor). The min. Ki and the max. f values were obtained for poly(DSG), and in the system of MetHb-H2O2-ABTS they were 0.08 .mu.M and 27.5, resp. According to their antiradical activities, the inhibitors can be arranged as follows: poly(DSG) > poly(ADSNP) > PG > **Trolox**, PG, poly(DSG), poly(ADSNP), and its conjugate with HSA are suggested as "calibrators", i.e., inhibition stds. for evaluation of antioxidant status of biol. fluids in possible test systems based on the free radical-generating pair MetMb-H2O2 with ABTS as the acceptor of the active radicals.
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

DLINE
ACCESSION NUMBER: 1999345778 MEDLINE
DOCUMENT NUMBER: 99345778 PubMed ID: 10409186
TITLE: Detection of a ferrylhemoglobin intermediate in an endothelial cell model after hypoxia-reoxygenation.
AUTHOR: McLeod L L; Alayash A I
CORPORATE SOURCE: Division of Hematology, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, Maryland 20892, USA.
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1999 Jul) 277 (1 Pt 2) H92-9.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990913
Last Updated on STN: 19990913
Entered Medline: 19990830

AB A cell culture model of bovine aortic endothelial cells attached to microcarrier beads was used to study the interaction of diaspirin cross-linked **hemoglobin** (an oxygen-carrying blood substitute) with hypoxia-reoxygenation. **Hemoglobin** (200 microM) and hypoxia-volume restriction (3-5 h), together and separately, caused toxicity in this model, as measured by decreased cellular replating efficiency. **Hemoglobin** (60 microM) caused a reduction in hydrogen peroxide concentration and an increase in lipid peroxidation above that induced by hypoxia alone. Incubation of **hemoglobin** with endothelial cells caused transient oxidation of **hemoglobin** to its highly reactive and toxic ferryl species after >/=3 h of hypoxia, followed by 1 h of reoxygenation. Lipid peroxidation, which may occur in the presence of ferrylhemoglobin, also occurred after 1 h of reoxygenation. **Hemoglobin** caused a dose-dependent decrease in intracellular glutathione concentration, suggesting that it caused an oxidative stress to the cells. However, addition of ascorbate, alpha-tocopherol, or **trolox** did not decrease **hemoglobin** oxidation in the presence of normal or hypoxic cells. It is concluded that diaspirin cross-linked **hemoglobin** forms a ferryl intermediate in the absence of any exogenously added oxidant and contributes to the oxidative burden experienced by endothelial cells after hypoxia-reoxygenation, a condition that is likely to be encountered during trauma and surgery when **hemoglobin** solutions are used as perfusion agents.

L5 ANSWER 28 OF 86 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:466533 CAPLUS
DOCUMENT NUMBER: 127:202662
TITLE: Phycobilin biosynthetic reactions in extracts of cyanobacteria
AUTHOR(S): Cornejo, Juan; Beale, Samuel I.
CORPORATE SOURCE: Division Biology Medicine, Brown University, Providence, RI, 02912, USA
SOURCE: Photosynthesis Research (1997), 51(3), 223-230
CODEN: PHRSDI; ISSN: 0166-8595
PUBLISHER: Kluwer
DOCUMENT TYPE: Journal
LANGUAGE: English

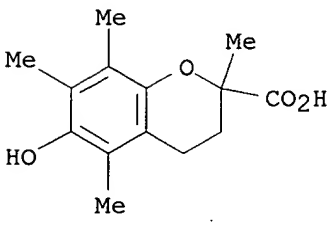
AB Phycobilins are the chromophores of phycobiliproteins, the light-harvesting pigments of cyanobacteria, red algae and cryptophytes. Phycobilins are biosynthesized from **heme** by the action of **heme** oxygenae, which converts **heme** to biliverdin, followed by the action of other enzymes that convert biliverdin to the phycobilins. The enzymes and biosynthetic intermediates of phycobilin formation in exts. of the unicellular red alga Cyanidium caldarium were previously reported. **Heme** oxygenase activity has not been obtained from exts. of the cyanobacterium Synechocystis sp. PCC 6701. The reaction requirements are similar to those for the C. caldarium enzyme: **heme** substrate, reduced ferredoxin, and a second reductant such as ascorbate or **Trolox**. The enzymic nature of the reaction was verified by two criteria in addn. to the requirement for cell ext.: prodn. of only the IX.alpha. isomer of the bilin product and inhibition by the substate analog Sn-protoporphyrin IX. The enzyme was partially purified by high-speed centrifugation, 35-75% differential (NH4)2SO4 pptn., and DEAE-cellulose anion exchange chromatog. In addn., ext. capoable of converting biliverdin IX.alpha. to phycobilins has been obtained from Synechocystis sp. PCC 6701 and another cyanobacterium, Synechocystis sp. PCC 6803. Only the (3Z) isomers of the phycobilins accumulated in the incubations contg. unfractionated cell exts., in contrast to incubations with unfractionated C. caldarium exts. which produce both the (3Z) and (3E) isomers. Physocyanobilin and phycoerythrobilin were produced in comparable amts. by Synechocystis sp. PCC 6701 exts., but only phycocyanobilin accumulated in Synechocystis sp. PCC 6803 exts. This difference in in vitro product accumulation correlates with the phycobilins that are found in vivo in these two cell types.

CCESSION NUMBER: 2001511032 MEDLINE
DOCUMENT NUMBER: 21442415 PubMed ID: 11555166
TITLE: Reaction of melatonin with **hemoglobin**-derived oxoferryl radicals and inhibition of the hydroperoxide-induced **hemoglobin** denaturation in red blood cells.
AUTHOR: Tesoriere L; Allegra M; D'Arpa D; Butera D; Livrea M A
CORPORATE SOURCE: Department of Pharmacological Sciences, University of Palermo, Italy.
SOURCE: JOURNAL OF PINEAL RESEARCH, (2001 Sep) 31 (2) 114-9. Journal code: 8504412. ISSN: 0742-3098.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20010918
Last Updated on STN: 20020305
Entered Medline: 20020304

AB Melatonin has been shown to act as a radical scavenger in various chemical and biological model systems in vitro. Kinetic evidence is now provided showing that melatonin inhibits the irreversible degradation of **hemoglobin** (**Hb**), when incubated with red blood cells exposed to the oxidant activity of cumene hydroperoxide (cumOOH). A decrease of **heme** loss and accumulation of soluble methemoglobin (met-**Hb**) are explained in terms of the interaction of the indoleamine with perferryl **Hb** (**Hb**[Fe(IV)=O]), a highly reactive **Hb**-derived radical species responsible for the irreversible **Hb** degradation. A kinetic study, in pure chemical solution, showed that melatonin can effectively reduce the oxoferryl **heme** group of perferryl-**Hb**, thus forming met-**Hb**. The reducing activity of melatonin is of the same order as that of **Trolox**, the water-soluble vitamin E analog. This novel radical-scavenging activity of melatonin may contribute to the previously observed protective effects of melatonin in ischemia-reperfusion injury.

L5 ANSWER 22 OF 86 MEDLINE

L1 ANSWER 4 OF 6 REGISTRY COPYRIGHT 2003 ACS
RN 53188-07-1 REGISTRY
CN 2H-1-Benzopyran-2-carboxylic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2H-1-Benzopyran-2-carboxylic acid, 3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-, (.+-.)-
OTHER NAMES:
CN (.+-.)-6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid
CN **(.+-.)-Trolox**
CN (R,S)-6-Hydroxy-2,5,7,8-tetramethyl-2-chromanecarboxylic acid
CN 6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid
CN **Trolox**
CN **Trolox C**
FS 3D CONCORD
DR 56305-04-5
MF C14 H18 O4
CI COM
LC STN Files: AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MSDS-OHS, NIOSHTIC, PIRA, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

481 REFERENCES IN FILE CA (1962 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
481 REFERENCES IN FILE CAPLUS (1962 TO DATE)

ACCESSION NUMBER: 1995:750975 CAPLUS
DOCUMENT NUMBER: 123:162901
TITLE: Assessment of **hemoglobin**-dependent neurotoxicity: alpha-alpha **crosslinked hemoglobin**
AUTHOR(S): Panter, S. S.; Vandegriff, K. D.; Yan, P. O.; Regan, R. F.
CORPORATE SOURCE: Letterman Army Inst. Res., Presidio of San Francisco, CA, USA
SOURCE: Report (1993), Order No. 362,257, 19 pp. Avail.: NTIS From: Gov. Rep. Announce. Index (U. S.) 1993, 93(20), Abstr. No. 362,257
DOCUMENT TYPE: Report
LANGUAGE: English

AB Adult human **Hb** Ao (HbAO) has been shown to be neurotoxic, and the authors wish to report on similar studies conducted using a modified **Hb** which has been **crosslinked** between the alpha subunits (alpha-alpha **Hb**). Cortical cell cultures were prepd. from fetal Swiss-Webster mice at 15-16 days gestation. Mature cultures (days in vitro, 12-16) were exposed to alpha-alpha **Hb** in a defined medium for 24-48 h at 37.degree.. Low micromolar amts. of alpha-alpha **Hb** were neurotoxic in a concn.-dependent fashion. This toxicity was attenuated by the antioxidants **Trolox** and U74500A and by the iron chelator deferoxamine. The **Hb**-binding protein, haptoglobin, also completely blocked alpha-alpha **Hb**-dependent neurotoxicity. The latter result was unexpected because complex formation between alpha-alpha **Hb** and haptoglobin was not detected using assays of haptoglobin fluorescence and **Hb** peroxidase activity.

IT Crosslinking
(neurotoxicity of alpha-alpha **crosslinked Hb**)

IT **Hemoglobins**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(neurotoxicity of alpha-alpha **crosslinked Hbs**)

IT Toxicity
(neurotoxicity, neurotoxicity of alpha-alpha **crosslinked Hbs**)

L7 ANSWER 8 OF 18 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:654245 CAPLUS
DOCUMENT NUMBER: 123:106126
TITLE: Phycobilin biosynthesis: reductant requirements and product identification for **heme** oxygenase from Cyanidium caldarium
AUTHOR(S): Rhie, Gi-eun; Beale, Samuel I.
CORPORATE SOURCE: Div. Biology and Medicine, Brown Univ., Providence, RI, 02912, USA
SOURCE: Archives of Biochemistry and Biophysics (1995), 320(1), 182-94
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Algal **heme** oxygenase is a sol. enzyme from Cyanidium caldarium that catalyzes the first committed step of phycobilin biosynthesis by converting protoheme to biliverdin IX.alpha.. Although the physiol. substrate (protoheme) of algal **heme** oxygenase is identical to that of microsomal **heme** oxygenase, which catalyzes **heme** catabolism in animals, the two enzyme systems differ in several respects including the nature of the required reductants and soly. of the enzymes. Addn. of the strong Fe3+ ion chelators, desferrioxamine and Tiron (4,5-dihydroxy-1,3-benzenedisulfonic acid), greatly increased the yield of solvent-extd. bilin product. The effect of the Fe3+ chelators was approx. equal whether they were added during or after the enzyme incubation. Postincubation treatment of the enzyme reaction mixt. with strong acid also greatly increased the product yield. Addn. of desferrioxamine to the reaction mixt. after the incubation was terminated caused the appearance of an absorption spectrum, indicating an increase in the concn. of free bilin product. Acid and Fe3+ chelators are known to cause dissocn. of Fe(III)-bilin complexes. These results indicate that the in vitro enzymic reaction product of algal **heme** oxygenase is a nonenzyme-**bound** Fe(III)-biliverdin IX.alpha. complex that is poorly extd. and/or quantitated unless it is first dissocd. Algal **heme** oxygenase required the simultaneous presence of both reduced ferredoxin and a second reductant such as ascorbate for activity. The requirement for L-ascorbate could be substituted by **Trolox** (**6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid**) or D-ascorbate, but not by dehydroascorbate or dithiothreitol. **Heme** oxygenase was purified over 200-fold from C. caldarium by differential (NH4)2SO4 pptn. and serial column chromatog. over reactive blue 2-Sepharose, DEAE-cellulose, Sephadex G-75, and ferredoxin-Sepharose.

IT Ferredoxins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**heme** oxygenase from Cyanidium caldarium requirement for)

IT 50-81-7, L-Ascorbic acid, biological studies 10504-35-5, D-Ascorbic acid 56305-04-5, **Trolox**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**heme** oxygenase from Cyanidium caldarium requirement for)

IT 7439-89-6, Iron, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(reductant requirements and product identification for **heme** oxygenase from Cyanidium caldarium)

IT 9059-22-7P, **Heme** oxygenase
RL: BPR (Biological process); BSU (Biological study, unclassified); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); PROC (Process)

(reductant requirements and product identification for **heme** oxygenase from Cyanidium caldarium)

IT 102136-63-0
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(reductant requirements and product identification for **heme** oxygenase from Cyanidium caldarium)

ACCESSION NUMBER: 1995:801048 CAPLUS
DOCUMENT NUMBER: 123:250353
TITLE: Chemiluminescence and EPR studies on the excitation site of ferric-**heme**-oxo complexes of natural and model **heme** systems
AUTHOR(S): Liu, Yang; Nohl, Hans
CORPORATE SOURCE: Institute Pharmacology Toxicology, Veterinary University Vienna, Vienna, A-1030, Australia
SOURCE: Photochemistry and Photobiology (1995), 62(3), 433-8
CODEN: PHCBAP; ISSN: 0031-8655
PUBLISHER: American Society for Photobiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Chemiluminescence was detected both in the reaction system of H2O2 plus **heme** proteins such as methemo- and metmyoglobin and ferric-protoheme complexes used as a model system. The intensity of chemiluminescence was found to be mediated by **ligand** binding to the sixth coordination site of the ferric-protoheme compds., e.g. chemiluminescence was not obsd. with the bisimidazole ferric-protoheme complex. On the other hand the pentacoordinated histidine ferric-protoheme complex exhibited strong light emission. Comparative studies with various **ligand-heme** compds. elucidated that light emission was inversely correlated with the binding strength of the resp. **ligand** at the sixth coordination site. The basic reaction mechanism causing the establishment of an excited state was studied by monitoring chemiluminescence and EPR signal formation of **ligand**-modified **heme** proteins in the presence of different electron donors. External electron donors such as **Trolox** C, TMPD and ascorbic acid affected a strong redn. in the development of chemiluminescence suggesting the essential involvement of an inner-mol. electron transfer process. Our results allow the conclusion that chemiluminescence is generated from the decay of an excited state of oxo-**heme** compds. established as a result of a one electron transfer step from a **ligand** group to **heme** iron.

IT Luminescence, chemi-
(chemiluminescence and EPR studies on the excitation site of ferric-**heme**-oxo complexes of natural and model **heme** systems)

IT Hemoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(chemiluminescence and EPR studies on the excitation site of ferric-**heme**-oxo complexes of natural and model **heme** systems)

IT **Hemoglobins**, met-
RL: RCT (Reactant); RACT (Reactant or reagent)
(chemiluminescence and EPR studies on the excitation site of ferric-**heme**-oxo complexes of natural and model **heme** systems)

IT Myoglobins, met-
RL: RCT (Reactant); RACT (Reactant or reagent)
(chemiluminescence and EPR studies on the excitation site of ferric-**heme**-oxo complexes of natural and model **heme** systems)

IT 50-81-7, Ascorbic acid, reactions 100-22-1, TMPD 7722-84-1, Hydrogen peroxide, reactions 56305-04-5, **Trolox** C
RL: RCT (Reactant); RACT (Reactant or reagent)
(chemiluminescence and EPR studies on the excitation site of ferric-**heme**-oxo complexes of natural and model **heme** systems)

IT 14875-96-8, **Heme**
RL: RCT (Reactant); RACT (Reactant or reagent)
(coordination of iron, chemiluminescence and EPR studies on the excitation site of ferric-**heme**-oxo complexes of natural and model **heme** systems)

IT 71-00-1, Histidine, reactions 288-32-4, Imidazole, reactions 7439-89-6, Iron, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)

(coordination of, chemiluminescence and EPR studies on the excitation site of ferric-**heme**-oxo complexes of natural and model **heme** systems)

L5 ANSWER 1 OF 86 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1981:531057 CAPLUS
DOCUMENT NUMBER: 95:131057
TITLE: Antioxidant activity of amino acids bound to **Trolox**-C
AUTHOR(S): Taylor, M. J.; Richardson, T.; Jasensky, R. D.
CORPORATE SOURCE: Sch. Pharm., Univ. Wisconsin, Madison, WI, 53706, USA
SOURCE: JAOCS, J. Am. Oil Chem. Soc. (1981), 58(5), 622-6
CODEN: JJASDH
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Amino acids, selected for their potential antioxidant activity, were covalently attached to **6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid** (**Trolox**-C) [56305-04-5], a lower homolog of vitamin E that has great antioxidant effectiveness. The resulting Troloxyl-amino acids (T-AA) had greater antioxidant effectiveness than **Trolox**-C in a linoleate emulsion system oxidized by **Hb**. Troloxyl-tryptophan-Me ester [78261-75-3] and Troloxyl-methionine-Me ester [78261-74-2] were the most effective T-AA evaluated in the linoleate emulsion. However, BHA, BHT, and .alpha.-tocopherol were more antioxidative than any T-AA in the emulsion system. In a Schaal oven test at 45.degree., **Trolox**-C was the most effective antioxidant evaluated in corn oil. BHT and Troloxyl-cysteine [78261-73-1] had significant antioxidant activity in corn oil, but no other T-AA had antioxidant activity in corn oil. In butter oil, **Trolox**-C again had the highest antioxidant activity, and BHA and BHT were also highly antioxidant. All T-AA had antioxidant activity in butter oil, with Troloxyl-methionine [78275-92-0] and Troloxyl-cysteine having the greatest antioxidant effectiveness. The T-AA of highest antioxidant activity were hydrolyzed by chymotrypsin and (or) trypsin, in vitro.

L5 ANSWER 2 OF 86 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:654245 CAPLUS
DOCUMENT NUMBER: 123:106126
TITLE: Phycobilin biosynthesis: reductant requirements and product identification for **heme** oxygenase from Cyanidium caldarium
AUTHOR(S): Rhie, Gi-eun; Beale, Samuel I.
CORPORATE SOURCE: Div. Biology and Medicine, Brown Univ., Providence, RI, 02912, USA
SOURCE: Archives of Biochemistry and Biophysics (1995), 320(1), 182-94
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Algal **heme** oxygenase is a sol. enzyme from Cyanidium caldarium that catalyzes the first committed step of phycobilin biosynthesis by converting protoheme to biliverdin IX.alpha.. Although the physiol. substrate (protoheme) of algal **heme** oxygenase is identical to that of microsomal **heme** oxygenase, which catalyzes **heme** catabolism in animals, the two enzyme systems differ in several respects including the nature of the required reductants and soly. of the enzymes. Addn. of the strong Fe3+ ion chelators, desferrioxamine and Tiron (4,5-dihydroxy-1,3-benzenedisulfonic acid), greatly increased the yield of solvent-extd. bilin product. The effect of the Fe3+ chelators was approx. equal whether they were added during or after the enzyme incubation. Postincubation treatment of the enzyme reaction mixt. with strong acid also greatly increased the product yield. Addn. of desferrioxamine to the reaction mixt. after the incubation was terminated caused the appearance of an absorption spectrum, indicating an increase in the concn. of free bilin product. Acid and Fe3+ chelators are known to cause dissocn. of Fe(III)-bilin complexes. These results indicate that the in vitro enzymic reaction product of algal **heme** oxygenase is a nonenzyme-bound Fe(III)-biliverdin IX.alpha. complex that is poorly extd. and/or quantitated unless it is first dissocd. Algal **heme** oxygenase required the simultaneous presence of both reduced ferredoxin and a second reductant such as ascorbate for activity. The requirement for L-ascorbate could be substituted by **Trolox** (**6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid**) or D-ascorbate, but not by dehydroascorbate or dithiothreitol. **Heme** oxygenase was purified over 200-fold from C. caldarium by differential (NH4)2SO4 pptn. and serial column chromatog. over reactive blue 2-Sepharose, DEAE-cellulose, Sephadex G-75, and ferredoxin-Sepharose.

L5 ANSWER 3 OF 86 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:202536 CAPLUS
DOCUMENT NUMBER: 122:3953
TITLE: Visible chemiluminescence associated with the reaction between methemoglobin or **oxyhemoglobin** with hydrogen peroxide
AUTHOR(S): Lissi, Eduardo A.; Escobar, Jorge; Pascual, Carlos; del Castillo, Maria; Schmitt, Tais H.; Di Mascio, Paolo
CORPORATE SOURCE: Fac. Cienc., Univ. Santiago de Chile, Santiago, Chile
SOURCE: Photochemistry and Photobiology (1994), 60(5), 405-11
CODEN: PHCBAP; ISSN: 0031-8655
PUBLISHER: American Society for Photobiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Visible chemiluminescence is emitted in the irreversible deactivation of **Hb** or metHb with excess H2O2. The emission takes place in 2 phases. The most intense phase lasts a few seconds and is followed by a 2nd phase of lower intensity that remains for longer periods. This 2nd phase presents chaotic or sustained oscillations. Free radicals are implicated in the luminescent process since the emission can be reduced by free radical scavengers such as **6-hydroxy-2, 5,7,8-tetramethylchroman-2 -carboxylic acid** (**Trolox**) or ascorbic acid. These additives lead to a delay in reaching the max. intensity, which can be related to their consumption, implying substantial recycling of the hemoprotein. Chemiluminescence is also obsd. in the oxidn. of hemin by H2O2, suggesting a role for the **heme** group in the processes leading to the excited state prodn. The lower intensity obsd. in the presence of hemin can be related to the contribution of the globin chains.

L5 ANSWER 4 OF 86 MEDLINE

ACCESSION NUMBER: 1993:17603 CAPLUS
DOCUMENT NUMBER: 118:17603
TITLE: The interaction of **Trolox** C, a water-soluble vitamin E analog, with ferrylmyoglobin: reduction of the oxoferryl moiety
AUTHOR(S): Giulivi, Cecilia; Romero, Francisco J.; Cadenas, Enrique
CORPORATE SOURCE: Inst. Toxicol., Univ. South. California, Los Angeles, CA, 90033, USA
SOURCE: Archives of Biochemistry and Biophysics (1992), 299(2), 302-12
CODEN: ABBIA4; ISSN: 0003-9861
DOCUMENT TYPE: Journal
LANGUAGE: English
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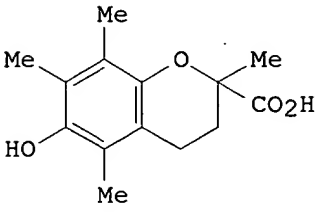

I

AB The interaction of **Trolox** (I), a water-sol. vitamin E analog, with ferrylmyoglobin entailed 2 sequential 1-electron oxidns. of the phenolic antioxidant with intermediate formation of a phenoxyl radical and accumulation of a quinone end product. These oxidn. reactions were **linked** to individual redns. of ferrylmyoglobin to metmyoglobin, as indicated by the value of the relationship [metmyoglobin]formed/[I]consumed: 1.92 .+-. 0.28. The I-mediated redn. of ferrylmyoglobin to metmyoglobin could proceed directly, i.e., electron transfer from the phenolic-OH group in I to the oxoferryl moiety, or indirectly, i.e., sequential electron transfer from I to a protein radical to the oxoferryl moiety. The former mechanism is supported by the finding that the high oxidn. **heme** iron is reduced under conditions where the tyrosyl residues are blocked by o-acetylation and when hemin is substituted for myoglobin. The latter mechanism is consistent with the following observations: (a) the EPR signal ascribed to the protein radical is suppressed by I, with the concomitant appearance of the EPR spectrum of the I phenoxyl radical and (b) the rate of ferrylmyoglobin redn. by I is decreased with increasing no. of tyrosyl residues in the proteins of horse myoglobin (titrated by o-acetylation) and sperm whale myoglobin. The apparent discrepancy between these observations can be reconciled by considering that both electrophilic centers in ferrylmyoglobin-the oxoferryl **heme** moiety and the protein radical-function independently of each other and that recovery of ferrylmyoglobin by I could be effected through the tyrosyl residues, albeit at slower rates. The mechanistic aspects of these results are discussed in terms of the 2 main redox transitions in the myoglobin mol. encompassing valence changes of the **heme** iron and electron transfer of the tyrosyl residue in the protein and **linked** to the 2 sequential 1-electron oxidns. of I.

IT Myoglobins, oxy-
RL: PRP (Properties)
(ferryl-, interaction of, with **Trolox** C)

IT 57028-37-2
RL: FORM (Formation, nonpreparative)
(formation of, in **Trolox** C-ferrylmyoglobin interactions)

IT 56305-04-5, **Trolox** C
RL: PRP (Properties)
(interaction of, with ferrylmyoglobins)